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## Vitamin D and Diabetes Let the Sunshine In

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### Abstract

Diabetes is a leading cause of cardiovascular disease. Persons with diabetes are at greater risk for early cardiac mortality, and for repeat events if they survive their first cardiac event. Recently, low serum concentrations of vitamin D have been associated with increased risk for cardiac events. Evidence indicates that persons with diabetes have lower serum concentrations of vitamin D. In addition, persons at risk for diabetes or metabolic syndrome have inadequate serum concentrations of vitamin D. This review will assess the evidence relative to the impact of vitamin D in the development of diabetes, metabolic syndrome, and diabetes complications. Studies that address vitamin D and its impact on metabolic outcomes as well as possible mechanisms of action are provided. Finally, the assessment and suggested treatment for vitamin D deficiency is addressed. Effective detection and treatment of inadequate vitamin D concentrations in persons with diabetes or those at risk for diabetes may be an easy and cost-effective therapy which could improve their long-term health outcomes as well as their quality of life.

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Proper nutrition is one of the most challenging issues for persons with diabetes. To be successful in the treatment of their disease and in the prevention of long-term complications, a diet that meets the daily requirements and is also satisfying to the individual is optimal. However, sometimes diet alone may not be sufficient for adequate intake of certain nutrients. Recently, vitamin D has sparked widespread interest because of its potential health benefits. Previously, research on vitamin D as it related to health outcomes was limited to persons with cancer and osteoporosis. Recently, however, its impact on other chronic illness has been examined.<sup>1,2</sup> Some information on vitamin D deficiency and the development of metabolic syndrome and diabetes has been reported.<sup>3–5</sup> However, specific information relative to its impact on metabolic control and complications in persons with diabetes has not been well addressed. This is an important area of study because many individuals with diabetes have decreased levels of vitamin D.<sup>5</sup> And, evidence suggests that lack of vitamin D may be associated with hyperglycemia, increased hemoglobin A1c, insulin resistance, progression of diabetes, as well as hypertension, and cardiovascular disease. Treatment of low vitamin D by diet and oral supplements may be an easy and cost-effective method to improve metabolic control and prevent the serious complications associated with diabetes.

### Vitamin D and Diabetes

The relationship between lack of vitamin D and diabetes (type 1 and 2) has been reported in the literature. Hyppönen et al<sup>6</sup> examined a birth cohort of pregnant women (n = 12 055) in Finland who were scheduled to give birth in 1966. One year later, there were 10 821 for follow-up, and 81 were diagnosed with type 1 diabetes. Vitamin D supplementation (regular

and irregular) was associated with a lower incidence of type 1 diabetes (24 and 33 per 100 000 years at risk, respectively) as compared with those who did not (204 per 100 000 years at risk). In addition, children who had a dose of 2000 IU daily (recommended dose at the time) had a decreased frequency of type 1 diabetes (Rate Ratio: 0.22; Confidence Interval, 0.05–0.89). In the EURODIAB study, 7 centers in Europe which had registries of patients with verified insulin-dependent diabetes examined patients for their eating habits (including vitamin D supplementation) and the risk of type 1 diabetes. Over 3000 patients (820 patients and 2335 controls) were studied. There was a decreased risk of type 1 diabetes in persons who had vitamin D supplementation (Odds Ratio, 0.67; CI, 0.53–0.86).<sup>7</sup> More recently, a meta-analysis of controlled trials and observational studies that assessed the effect of vitamin D supplementation on risk of type 1 diabetes included 5 studies. Of these, 1 was a cohort study and the other 4 were case-control studies. For the case-control studies, evidence indicated that there was significantly lower incidence of type 1 diabetes in infants who got supplemental vitamin D (Odds Ratio, 0.71; CI, 0.60–0.84). The cohort study supported this finding. It was concluded that vitamin D supplementation may be protective against type 1 diabetes; however, randomized clinical trials are necessary to establish cause, dose, and duration.<sup>8</sup>

For persons with type 2 diabetes, it has been reported that females with type 2 diabetes have a high prevalence of hypovitaminosis D.<sup>9</sup> Several studies, particularly in women, have suggested that low vitamin D concentration is associated with increased risk for diabetes and metabolic syndrome. Assessment of serum vitamin D is done by measuring concentrations of 25 hydroxyvitamin D, also known as 25 (OH) D.<sup>2</sup> Scragg et al<sup>10</sup> examined the National Health and Nutrition Examination Survey (NHANES) III sample (1988–1994) for serum levels of 25 (OH) D, fasting and/or 2-hour plasma glucose, and insulin. The odds ratio of diabetes was 0.25 (CI, 0.11–0.60) for non-Hispanic Whites, and 0.17 (CI, 0.08–0.37) for Mexican Americans when the highest quartile was compared with the lowest quartile for vitamin D levels. In addition, insulin resistance (measured by homeostasis model, HOMA) was inversely associated with vitamin D levels for Mexican Americans ( $P = .0024$ ), and whites ( $P = .058$ ). These relationships were not found for blacks, and it was suggested that this may be due to a decreased sensitivity to vitamin D in this population.

In the Mini-Finland Health Study (1978–1980),<sup>11</sup> men and women ( $n = 4423$ ) aged 40 to 69 were followed for 17 years to determine incident cases of type 2 diabetes ( $n = 187$ ). Relative risk for diabetes was 0.60 (CI, 0.36–0.98;  $P$  trend = .01) and 0.70 (CI, 0.42–1.16;  $P$  trend = .07) after adjustments for body mass index, leisure time exercise, smoking, and education when highest and lowest serum 25 (OH) D concentrations were compared. In the Nurses Health Study,<sup>4</sup> which included over 84 000 women with no history of diabetes at baseline, there were 4843 incident cases of diabetes over 20 years. The relative risk of diabetes was 0.87 (CI, 0.75–1.00;  $P$  trend = .04) when comparing highest (800 IU) with lowest (400 IU) supplementation of vitamin D.

In terms of metabolic syndrome, Liu and colleagues<sup>12</sup> reported that in the Women's Health Study ( $n = 10\ 066$ ), poor dietary intake of vitamin D was significantly associated with metabolic syndrome, but was dependent on total calcium intake. Ford et al<sup>13</sup> examined participants from NHANES III (1998–1994) who had metabolic syndrome, defined according to National Cholesterol Education Program criteria, and a measurement of 25 (OH) D. The prevalence of metabolic syndrome was 21.9%. The odds ratio of having metabolic syndrome decreased with increasing concentrations of vitamin D when examined by quintiles (0.81, 0.67, 0.62, 0.50, 0.38,  $P < .001$ ). Even, after excluding persons with diabetes, the finding was consistent. A limitation was the cross-sectional nature of the study and a single measurement of vitamin D. For participants from the Rancho Bernardo Study ( $n = 1070$ ), it was reported that increasing parathyroid levels increased risk for metabolic

syndrome in men, not women. They reported no effect of 25 (OH) D levels in either sex for metabolic syndrome; however, the levels of vitamin D were normal to above normal for this group.<sup>14</sup>

Recently, a meta-analysis for both observational studies and clinical trials examined vitamin D and calcium homeostasis as it relates to type 2 diabetes.<sup>5</sup> Observational studies demonstrated that low vitamin D, calcium, or dairy was associated with greater prevalence of type 2 diabetes or metabolic syndrome. For type 2 diabetes, the odds ratio was lower 0.36 (CI, 0.16–0.80) for individuals who had the highest as compared with the lowest 25 (OH) D concentrations. This relationship was also present for incident type 2 diabetes (0.82, CI, 0.72–0.93) for vitamin D and calcium intake. Evidence from observational studies and clinical trials indicates that vitamin D and/or calcium supplementation may be important in the prevention of type 2 diabetes, particularly for those with glucose intolerance.

## Vitamin D and Complications of Diabetes

Diabetes is associated with complications such as cardiovascular disease, renal impairment, and peripheral neuropathies. Studies have explored the relationship of vitamin D concentrations to these complications; however, many of these have not been studied in persons with diabetes. The earliest evidence for the relationship of vitamin D concentration to cardiovascular disease began with patients who had end stage renal disease. It was found that in persons having dialysis that cardiovascular mortality was 10 to 20 times higher than the general population. The severe hypertension in these patients was attributed to the reduced synthesis of calcitriol by the kidneys. When patients were given 1 alpha-vitamin D and the vitamin D analogue paricalcitol, it was noted that the mortality rate for cardiovascular disease was significantly reduced.<sup>15</sup>

The relationship between vitamin D levels and hypertension has been explored. Forman et al<sup>16</sup> examined 2 cohorts, 1 from Health Professionals' Follow-Up Study and another from Nurses' Health Study, at several points in time. The relative risk of hypertension was 6.13 (CI, 1.00–37.8) for men, and 3.18 (CI, 1.39–7.29) for men and women when levels of vitamin D deficiency (< 15 ng/mL) were compared with those with sufficient levels (≥30 ng/mL). It has been suggested that insufficient vitamin D may also be a reason for hypertension due to stimulation of the renin-angiotensin system. Evidence has indicated that treatment with calcitriol may reduce the activation of the renin-angiotensin system.<sup>15</sup>

In terms of cardiovascular disease, Wang et al<sup>17</sup> examined participants of the Framingham Offspring study (n = 1739) who did not have cardiovascular disease at the time of enrollment. At baseline, the mean age was 59, all were white, and 55% were women. The mean 25 (OH) D level was 19.7 ng/mL, and 37% of persons had levels ≤ to 15 ng/mL. At a mean follow-up of 5.4 years, 120 participants had suffered a cardiovascular event. Levels of 25 (OH) D of <15 ng/mL were associated with a greater risk for cardiovascular events after adjustment for age and sex (Hazards Ratio: 2.04; CI, 1.42–2.94; *P* < .001). With further adjustment for cardiovascular risk factors and renal function, risk for cardiovascular events was still increased (1.62; CI, 1.11–2.36; *P* = .01). Similar findings existed after an adjustment for physical activity, vitamin D supplementation, season, and level of education (1.70; CI, 1.08–2.67; *P* = .02). When models were created to examine the following categories of vitamin D concentrations (≥15, 10–15, and <10 ng/mL), the hazards ratio demonstrated a linear trend (1.00, 1.53, and 1.80, *P* = .01) for increased cardiovascular risk. The authors suggest that correction of D deficiency may be important for prevention of cardiovascular disease. A recent meta-analysis of 18 randomized, controlled trials for vitamin D noted that intake of ordinary supplemental doses of vitamin D (from 300 IU to 2000 IU) was associated with a reduced risk of mortality (RR, 0.93; CI, 0.87–0.99).<sup>18</sup> The

authors suggested that placebo-controlled randomized trials need to be conducted and that the relationship between the baseline vitamin D, dose of vitamin D supplementation, and other health outcomes.

Renal insufficiency is another real unfortunate complication of living with diabetes. Recently, Wolf et al<sup>19</sup> studied 825 US hemodialysis patients (175 who died within 90 days and who were compared to 750 who survived) to determine the relationship between vitamin D levels and mortality. They reported that 78% of the patients were vitamin D deficient and that this was associated with an increased early mortality. For individuals with 25 (OH) D levels <10 ng/mL, the odds ratio was 1.9 (CI, 1.3–2.9) and for those with levels between 10 and 30 ng/mL, it was 1.4 (CI, 1.0–2.0). Zhang et al<sup>20</sup> reported that receptor-mediated vitamin D actions may be protective of kidneys in rats with diabetic nephropathy. This suggests that perhaps vitamin D may be useful and preventative for the kidneys. Chonchol and Scragg<sup>21</sup> studied the relationships between serum levels of 25 (OH) D, insulin resistance, and kidney function in NHANES III participants (n = 14 679). The level of 25 (OH) D was significantly lower in persons with severely decreased glomerular filtration rate when compared with those with normal kidney function. In addition, persons in this study with higher levels of 25 (OH) D had decreased insulin resistance (HOMA–IR).

Finally, diabetic neuropathy has been associated with low concentrations of vitamin D.<sup>22</sup> A small, clinical study of 51 patients with type 2 diabetes (37 female) were evaluated for neuropathic complaints such as pain, burning, tingling, numbness, and throbbing sensations. They assessed pain using both the McGill pain questionnaire and a visual analog scale, and serum 25 (OH) D levels were drawn. Patients who were vitamin D deficient were given cholecalciferol (D<sub>3</sub>) (mean does 2059 IU) and re-evaluated at 3 months follow-up. Serum concentrations increased 67.4% ( $P < .05$ ) from 18 to 30 ng/mL, and were associated with significantly lower pain scores ( $P < .05$ ). Given these findings, the use of vitamin D for treatment of neuropathic pain needs further study.

## Vitamin D and Metabolic Outcomes

Studies have been conducted on persons to determine the effect of vitamin D on fasting glucose, insulin secretion and sensitivity, and hemoglobin A1c. Most of these were limited by a small sample size. One of the earliest studies was conducted by Ljunghall et al<sup>23</sup> who studied 65 middle-aged men with impaired glucose tolerance. They reported that vitamin D levels were not associated with a change in glucose, insulin or HBA1c, however, their subjects had normal levels of vitamin D. A later study which examined 34 middle-aged men (of which 7 had diet-managed diabetes) and metabolic risk factors demonstrated that serum levels of 25 (OH) D were correlated to fasting insulin ( $r = -.35$ ;  $P < .05$ ) and to insulin sensitivity ( $r = .54$ ;  $P < .001$ ).<sup>24</sup>

Orwoll et al<sup>25</sup> studied 35 (23 males) subjects who had diabetes and were on oral hypoglycemic agents. They examined the relationship between vitamin D and glucose regulation using 2 protocols. In protocol #1, diabetes medication was stopped for 7 days and levels of vitamin D, fasting glucose, insulin, c-peptide, glucagon were measured. However, no relationship was found among these measurements. In protocol #2, they administered 1, 25 dihydroxyvitamin D (1 µg per day for 4 days), and reported no change in insulin or glucose handling. A limitation of this study was the small sample and that the levels of vitamin D for the subjects were within the low to normal range at onset. In a larger sample of elderly men (n = 142), Baynes et al<sup>26</sup> reported that abnormal oral glucose testing was inversely associated with serum concentrations of 25 (OH) D ( $r = -.23$ ;  $P = .01$ ). In addition, insulin concentrations were also associated with concentrations of 25 (OH) D ( $r = -.18$ ;  $P < .05$ ). A limitation of all of these studies was that mostly men were studied.

Chiu and colleagues<sup>27</sup> studied a group (n = 126) of healthy, glucose-tolerant subjects (58% women) who were assessed for insulin sensitivity and beta cell function using hyperglycemic clamps. They reported that 25 (OH) D levels were positively associated with insulin sensitivity ( $P < .0001$ ) and negatively with first and second phase insulin response ( $P = .0045$  and  $P < .0001$ , respectively). A negative association was also found between 25 (OH) D concentration and glucose concentration at fasting ( $P = .0258$ ), 60 minutes ( $P = .0011$ ), 90 minutes ( $P = .0011$ ) and 120 minutes ( $P = .0007$ ) during the glucose tolerance test. They concluded that low vitamin D concentrations were associated with insulin resistance and beta cell dysfunction. More recently, Need et al<sup>28</sup> reported that in 753 postmenopausal women with no known glucose abnormality serum 25 (OH) D levels were negatively associated with fasting serum glucose ( $r = -.15$ ;  $P < .001$ ). In addition, the greatest increase in blood sugar was noted in those with 25 (OH) D levels below 40 nmol/L.

Borissova et al<sup>29</sup> reported that vitamin D deficiency contributes to impaired insulin secretion and probably insulin action. They studied 10 women with type 2 diabetes and 17 female controls (no diabetes, matched on age and body mass index). Persons with type 2 diabetes were given 1332 IU daily of vitamin D (cholecalciferol) for 1 month. They reported a 21.4% decrease in insulin resistance after 1 month. They also reported that both the first phase insulin secretion, as well as the second phase insulin secretion, decreased by 34% and 20%, respectively, in the group with diabetes when compared with the controls. This study suggested that vitamin D supplementation may have positive metabolic effects for persons with diabetes.

Most recently, Pittas et al<sup>30</sup> conducted a double blind randomized controlled trial in nondiabetic adults (n = 314) who received 500 mg of calcium citrate with 700 IU D<sub>3</sub> daily or placebo for a period of 3 years. For individuals with impaired fasting glucose at baseline who received the supplement, they had a lower rise in fasting plasma glucose ( $P = .042$ ) and a lower increase in insulin resistance (HOMA-IR;  $P = .031$ ) when compared with those who took placebo. Therefore, the combined effect of calcium and vitamin D was beneficial for metabolic outcomes in those with impaired glucose, and may be a promising treatment for those at risk for diabetes.

Suzuki et al<sup>31</sup> reported on the microvascular complications associated with type 2 diabetes in the presence of hypovitaminosis. In this observational study of Japanese patients with type 2 diabetes (n = 581) and controls (n = 51), the mean level of 25 (OH) D was 17 ng/mL with greater concentrations in men as compared with women (18.6 vs. 15.1 ng/mL). Of concern was that over 70% of the sample had concentrations that were indicative of hypovitaminosis (<20 ng/mL). There was a significant relationship between serum 25 (OH) D concentration and HBA1c ( $r = -.512$ ,  $P = .013$ ) as well as the number of diabetes complications ( $r = -.669$ ,  $P = .027$ ).

## Vitamin D and Possible Mechanisms of Action

The mechanisms whereby vitamin D may impact on the development and management of diabetes are important areas of research. It has been reported that insulin secretion is dependent upon vitamin D in animals and isolated islets.<sup>32</sup> It has also been reported that vitamin D deficiency reduces insulin secretion.<sup>29,32</sup> In addition, recent data has demonstrated the presence of vitamin D receptors on the beta cells of the islets of Langerhans, and the ability of the islets to express 1-alpha hydroxylase thereby activating 25 (OH) D. An indirect effect of vitamin D on beta cell insulin secretion is also postulated by means of increased intracellular calcium in the islet.<sup>5,33</sup> Vitamin D receptors have also been identified in cells of the immune system. In studies of nonobese diabetic mice, high doses of 1 alpha 25-dihydroxyvitamin D<sub>3</sub> (active form of vitamin D) have been shown to delay the

onset of diabetes by means of immune modulation.<sup>34</sup> This active form has been shown to protect beta cell function caused by inflammatory cytokines (IL-6 and TNF-alpha).<sup>35</sup> IL-6 has been noted to inhibit insulin receptor signal transduction, and administration of this cytokine has been associated with hyperglycemia and hyperinsulinemia.<sup>35</sup> Recent evidence has demonstrated that persons with type 2 diabetes who have hypovitaminosis D are more likely to have increased CRP ( $P = .001$ ), fibrinogen ( $P = .001$ ), and A1c ( $P = .01$ ) compared with those persons with diabetes who do not.<sup>36</sup> Therefore, understanding the role that vitamin D receptors play in immune function for the development and progression of diabetes will be an important area of future research.

Genetic variations in vitamin D receptors maybe associated with risk of diabetes. Chang et al<sup>37</sup> identified vitamin D receptor polymorphisms which were associated with type 1 diabetes in a Taiwanese population. In the Rancho Bernardo Cohort, it was reported that in nondiabetic Caucasians, 1 polymorphism (Apal) was associated with glucose intolerance, while another (Bsmal) was associated with insulin resistance.<sup>38</sup> A link has been identified between vitamin D receptor polymorphisms and type 2 diabetes; however, these findings differ depending on the population.<sup>34</sup> Most recently, variations in the CYP2R1 (vitamin D 25-hydroxylase) gene, which encodes for an enzyme that catalyzes the formation of the main vitamin D metabolite, has been associated with lower levels of vitamin D and type 1 diabetes.<sup>39</sup>

## Assessment of Vitamin D Status

Persons with diabetes are at significant risk for vitamin D insufficiency or deficiency. Reasons for this include diet, lack of sun exposure, obesity, renal impairment, and genetic predisposition (Table 1). As stated earlier, vitamin D status is best assessed by serum by 25 (OH) D. Some variation exists related to cutoff values for insufficiency and deficiency due to differences in assay methods and population variations.<sup>40</sup> Normal 25 (OH) D levels should be 30 to 60 ng/mL.<sup>2</sup> Vitamin D insufficiency has been reported to range from levels of 16 to 30 ng/mL.<sup>40,42</sup> Vitamin D deficiency is generally defined as levels of < 20 ng/mL.<sup>41</sup> The National Health and Nutrition Examination Survey (NHANES) III used a slightly lower level of <15 ng/mL.<sup>43</sup> A physiologic response to low serum vitamin D concentrations by increased parathyroid hormone indicates vitamin D deficiency and skeletal risk. The serum 25 (OH) D level causing increased parathyroid hormone may be used to assess vitamin D deficiency. However, with recent research relating vitamin D to diabetes, cardiovascular and auto-immune diseases, other biomarkers such as calcium absorption, insulin secretion, and immune response are being studied to establish optimal vitamin D status.<sup>44</sup>

Due to the dual sources of sun-mediated skin production and dietary intake, assessment of vitamin D status necessitates consideration of latitude, season, skin pigmentation, food, and supplemental sources. Because the primary source of this nutrient is skin production, assessment based on sun exposure provides insight into those at risk.<sup>44</sup> It is estimated that over 1 billion people have either vitamin D insufficiency or deficiency.<sup>2</sup> Recent reports of rickets in African American children have been followed by reports of vitamin D insufficiency and deficiency in adults. Using NHANES III data, the prevalence of hypovitaminosis D in women 15 to 49 years was 42.4% in African Americans compared with 4.2% in white women.<sup>43</sup> Of interest, seasonal variations in vitamin D status have been identified in adults residing in both upper and lower latitudes. In a Canadian study, 34% of adults had one 25 (OH) D level within a year that qualified as vitamin D insufficient.<sup>42</sup> In adults residing in South Florida and Hawaii, vitamin D deficiency has been reported to range from 38–51% with 13% seasonal fluctuation in serum 25 (OH) D levels.<sup>40,45</sup> Uninsured women have been identified as a vulnerable population as evidenced by a 67% prevalence of

vitamin D deficiency in a sample of 96 women aged 21 to 65 in Michigan. Non-Caucasians were 3.22 times more likely and those with vitamin D intakes < 400 IU per day were 10.2 times more like to be vitamin D deficient.<sup>46</sup>

Clinical manifestations of vitamin D deficiency vary depending on the severity. In children, classic vitamin D deficiency is termed rickets. The hallmark clinical manifestation is bowed legs due to disruption of bone mineralization and widening of the epiphyseal plates of the long bones.<sup>1</sup> This is often accompanied by growth retardation and “rachitic rosary” due to costochondral junction abnormalities. Because vitamin D deficiency in adults occurs after skeletal maturation and the fusing of the epiphyseal plates, clinical manifestations are different though still serious. Individuals with mild deficiency may be asymptomatic.<sup>47</sup> Adults with moderate to severe vitamin D deficiency, or osteomalacia, may experience muscle weakness, bone pain, difficulty walking especially stairs and more falls.<sup>1,47</sup> These can lead to progressive loss of bone, increased risk of fracture, and may be contributing factors to osteoporosis and osteopenia.<sup>1</sup> The complaint of bone pain is a distinction between osteoporosis and osteomalacia.<sup>48</sup>

## Dietary Implications of Vitamin D

Vitamin D is a fat-soluble vitamin that is consumed as ergocalciferol (D<sub>2</sub>) or cholecalciferol (D<sub>3</sub>) through dietary sources. The dietary reference intakes include values for adequate intakes and tolerable upper intake level for vitamin D which is summarized in Table 2.<sup>49</sup> Adequate intake levels were established based on adequate serum 25 (OH) D levels. The upper intake level is the maximum daily nutrient intake that is not likely to be associated with adverse effects for most people. Upper intake levels were established at the point when hypercalcemia occurs. A recommended dietary allowance (RDA) has not been established for this nutrient due to lack of adequate data. The need for revision of the vitamin D dietary reference intakes is currently a focus of scientific research and discussion.<sup>50</sup>

There are few foods that are naturally rich in vitamin D. These include fatty fish, some fish liver oil, and eggs from hens fed vitamin D. Milk products, breakfast cereals, infant formula, and juice can be good sources if fortified with vitamin D. Milk provides between 45 to 47% of dietary vitamin D intake by Americans.<sup>51</sup> Fortification of milk with vitamin D provides 10 µg (400 IU) per quart in the United States.<sup>49</sup> Most cheeses and other dairy products are not fortified with vitamin D. Table 3 summarizes vitamin D content and adequate intake for 2 age groups of adults of some common foods.<sup>52</sup> Dietary intake of US adults was estimated using NHANES III (1988–1994).<sup>51</sup> In this sample, only 10% of older adults (51–70) and 2% of the elderly (70+ years) met the adequate intake for vitamin D by food alone. Dietary supplements containing vitamin D increased the percentage of individuals having adequate intake by 10% to 25%. Barriers to consuming adequate dietary vitamin D include lactose intolerance, high mercury levels in fish, and energy restriction which is common for those with type 2 diabetes.

## Treatment of Vitamin D Deficiency

Considering the high prevalence of vitamin D deficiency and limited natural vitamin D food sources, recommendations for treatment of low 25 (OH) D include supplementation, food fortification and exposure of skin to ultraviolet light in safe doses and through effective mechanisms.<sup>53</sup> Supplemental doses that approximate the adequate intake (400 IU vitamin D per day) result in small increases in serum 25 (OH) D levels.<sup>53</sup>

Holick recommends a standard supplementation protocol for nonpregnant adults to treat vitamin D deficiency using a 2-phase protocol. The initial phase is a weekly dose of 50 000 IU vitamin D<sub>2</sub>, in 1 capsule, for 8 weeks.<sup>2</sup> After the initial phase, serum 25 (OH) D levels

should be evaluated and ideally be  $>30$  ng/mL. If this minimal serum level has not been achieved, then the initial phase may need to be repeated. This provides an average of 7152 IU D<sub>2</sub> per day. The second phase is a 50 000 IU capsule of vitamin D<sub>2</sub> every 2 to 4 weeks ongoing. Individuals with malabsorption syndromes, obesity, nephrotic syndrome, or those using medications that activate steroid or xenobiotic receptors may require an extended initial phase.<sup>2</sup> Other conditions such as hyperparathyroidism or granulomatous disorders require special consideration in treating vitamin D deficiency. Specific recommendations for vitamin D intake for those with diabetes, with or without vitamin D deficiency, have yet to be determined.<sup>5</sup>

Daily doses to correct deficiency would be 1000 IU vitamin D<sub>3</sub> or 3000 IU vitamin D<sub>2</sub>.<sup>2,54</sup> Considering that the half-life of vitamin D is 1 to 2 months, a third alternative for therapeutic dosing is 100 000 IU vitamin D<sub>3</sub> every 3 months.<sup>2,54</sup> This is common in Europe and called “stoss” therapy meaning “to bump” in German.<sup>55</sup> In African American postmenopausal women, Talwar et al<sup>56</sup> developed an algorithm of vitamin D<sub>3</sub> supplementation to achieve optimal serum concentrations which included a dose of 2800 IU per day if serum 25(OH)D was  $>45$  nmol/L (18 ng/mL) or 4000 IU per day if serum 25(OH)D was  $<45$  nmol/L (18/ng/mL).

Vitamin D<sub>3</sub> that is produced subcutaneously from exposure to sun or ultraviolet B radiation (UVB) from tanning bed or other devices can be stored in adipose tissue and released during times when intake or production is limited, such as winter months. Depending on seasonal variation, it is estimated that 5 to 30 minutes of sun exposure to arms and legs during mid-day is adequate to gain D<sub>3</sub> activity. For those with fat malabsorption, which may decrease vitamin D availability, safe exposure to UVB with adherence to therapeutic protocols has been recommended to treat vitamin D deficiency.<sup>57</sup> A recent study, however, reported that in persons who were 65 and older, sun exposure did not affect the inverse association that exists between percent body fat and low vitamin D levels.<sup>58</sup> This suggests that increased sun exposure, particularly in persons who are obese, may not be effective and could possibly put them at risk for other health problems.

Fortified foods are beneficial in increasing dietary intake of vitamin D and should be encouraged as a component in the treatment plan in combination with supplements and safe sun exposure. However, it is unlikely that 25 (OH) D levels could be corrected in a timely or effective manner with dietary sources alone.

## Summary

Vitamin D is an important nutrient for all persons, particularly for those with diabetes. Epidemiologic evidence suggests that an adequate intake of vitamin D may prevent or delay the onset of diabetes. There is also evidence to indicate that it may help to reduce some of the complications associated with diabetes (cardiovascular disease, renal insufficiency, and peripheral neuropathies). Small clinical studies have demonstrated that vitamin D may help with metabolic control, particularly as it relates to beta cell function. The information regarding vitamin D receptor activity as well as the genetic variations that may predispose individuals to problems with vitamin D synthesis and utilization will be important areas of clinical research.

It appears that diet alone will not provide sufficient amounts of vitamin D, and that treatment with supplements is probably necessary for most individuals with diabetes. However, given the possible benefit, it may be an easy and cost-effective therapy which could improve their long-term health outcomes as well as their quality of life.

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**Table 1**

## Factors Contributing to Low Vitamin D Levels in Diabetes

Dietary intake	Limited intake of foods high in vitamin D
Sun Exposure	Lack of outdoor physical activity due to possible fatigue, obesity, and or mobility issues
Obesity <sup>a</sup>	More vitamin D is stored in the fatty tissues and less is biologically active in the serum
Renal Insufficiency	Less biologically active vitamin D since conversion to the active form occurs in the kidneys
Genetic variations	Polymorphisms of vitamin D binding protein Polymorphisms of CYP2R1 gene (which is necessary to catalyze the formation of the main circulating vitamin D metabolite)

<sup>a</sup> Obesity is associated with inflammation, but low levels of vitamin D are also associated with inflammation. Cytokines and other inflammatory agents have been linked to beta cell damage which then impairs insulin synthesis and secretion.

**Table 2**

## Dietary Reference Intakes for Vitamin D by Life Stage Group

	<b>DRI Values (µg/day)</b>	
	<b>AI<sup>a,b,c</sup></b>	<b>UL<sup>d</sup></b>
<i>Life stage group<sup>e</sup></i>		
0 through 6 mo	5	25
7 through 12 mo	5	25
1 through 3 y	5	50
4 through 8 y	5	50
9 through 13 y	5	50
14 through 18 y	5	50
19 through 30 y	5	50
31 through 50 y	5	50
51 through 70 y	10	50
> 70 y	15	50
<i>Pregnancy</i>		
≥ 18 y	5	50
19 through 50 y	5	50
<i>Lactation</i>		
≥ 18 y	5	50
19 through 50 y	5	50

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<sup>a</sup> AI = Adequate Intake.

<sup>b</sup> As cholecalciferol. 1 µg cholecalciferol = 40 IU vitamin D.

<sup>c</sup> In the absence of adequate exposure to sunlight.

<sup>d</sup> UL = Tolerable Upper Intake Level. Unless otherwise specified, the UL represents total intake from food, water, and supplements.

<sup>e</sup> All groups except Pregnancy and Lactation represent males and females.

**Table 3**

## Vitamin D Content and % Adequate Intake (AI) of Common Foods

Food	µg per Serving	% AI for Adults 19–50 Years	% AI for Adults 51–70 Years
Salmon, 3.5 ounces	9.0	180	90
Tuna, in oil, 3 ounces	5.0	100	50
Milk, skim, vitamin D fortified, 1 cup	2.45	49	24.5
Margarine, vitamin D fortified, 1 tablespoon	1.5	30	15
Cereal, ready-to-eat			
Vitamin D fortified, ¾ cup	1.0	20	10
Egg, 1 whole	.5	10	5
Orange juice, vitamin D fortified, 8 ounces	2.0	50	20

Source: Adapted from <http://dietary-supplements.info.nih.gov/factsheets/vitamind.asp>